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(54) Title: TREATMENT OF DIABETIC RETINOPATHY

(57) Abstract

The use of compositions of antagonists of glutamate induced excitotoxicity for the treatment of diabetic retinopathy is disclosed.

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TREATMENT OF DIABETIC RETINOPATHY

This invention relates to the use of suitable antagonists of glutamate-induced excitotoxicity for the treatment of diabetic retinopathy, particularly that of the proliferative type.

Background of the Invention

Ambati, et al., "Elevated GABA, Glutamate, and VEGF in the Vitreous of Humans With Proliferative Diabetic Retinopathy," *Invest. Ophthalmol. Vis. Sci.*, 38:S771, 1997, reported elevated levels of glutamate in vitreous samples obtained from patients with proliferative diabetic retinopathy who underwent pars plana vitrectomy. They suggested that these levels of glutamate are potentially toxic to retinal ganglion cells.

Lieth, et al., "Glial Glutamate to Glutamine Conversion is Impaired in Retinas of Diabetic Rats," *Invest. Ophthalmol. Vis. Sci.*, 38:S695, 1997, reported that glial glutamate to glutamine conversion is impaired in the retinas of diabetic rats.

Hudson, et al., "Short-Wavelength and White-on-White Automated Static Perimetry in Patients With Clinically Significant Diabetic Macular Oedema (DMO)," *Invest. Ophthalmol. Vis. Sci.*, 38:S768, 1997, reported deficits in retinal function related to ganglion cell function in patients with diabetic macular edema.

Panretinal photocoagulation and the dietary and/or pharmacological control of hyperglycemia are the only methods currently in use to treat diabetic retinopathy. Vision loss is associated with the use of panretinal photocoagulation. Consequently, there is a need for new ways for treating diabetic retinopathy. The present compositions and methods fill that need.

Summary of the Invention

The present invention is directed to compositions and methods for treating diabetic retinopathy using an antagonist of the excitatory amino acid receptors involved in glutamate-induced excitotoxicity. In particular, N-methyl-D-aspartate (NMDA) receptor antagonists and more particularly antagonists of the polyamine receptor are useful for treating diabetic retinopathy.

Description of Preferred Embodiments

This invention provides a pharmacological method for preventing further damage to retinal ganglion cells resulting from diabetes and associated with glutamate-induced excitotoxicity. It is expected to be used instead of panretinal photocoagulation and thus avoid the near-term loss of vision that accompanies such photocoagulation.

The invention is a treatment for diabetic retinopathy, particularly of the proliferative type, comprising the local or systemic administration of a suitable antagonist of the excitatory amino acid receptors involved in glutamate-induced excitotoxicity. The purpose is to prevent damage to retinal ganglion cells resulting from the excitotoxic effects produced by excessive glutamate found in the retinas of patients who have proliferative diabetic retinopathy. A suitable glutamate antagonist is one which has the appropriate physicochemical properties to allow it to gain access to the site of action, i.e., the retina, following administration, either locally to the eye or systemically, of a pharmaceutically effective amount of such antagonist. The glutamate antagonist can work directly or indirectly to prevent the sequence of cellular events that ensues from the action of glutamate upon excitatory amino acid receptors at which glutamate can act. Glutamate receptors are classified as NMDA and non-NMDA receptors.

This invention includes antagonists that act on NMDA and non-NMDA receptors for glutamate. Particularly preferred antagonists are those which act on the NMDA receptor-calcium channel complex. Such antagonists may act by competing with glutamate at the receptor site, may act at one or all of several regulatory or modulatory sites associated with the NMDA receptor-calcium channel complex, or can inhibit one or more of the downstream effects that result from activation of the NMDA receptor-calcium channel complex. Examples include, but are not limited to, polyamine site antagonists, receptor antagonists (compete with NMDA), and channel blockers that operate uncompetitively to block the NMDA receptor channel.

Polyamine site antagonists are particularly useful according to this invention. Examples of specific examples are set out in U.S. Patent No. 4,690,931, which is incorporated herein by reference. The most preferred compounds in the patent are 2-[4-(4-fluorobenzyl)-piperidino]-1-(4-chlorophenyl)ethanol, also known as eliprodil and 2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-propanol, also known as ifenprodil.

Other compounds which are particularly useful include remacemide and memantine.

Because the site of action is located within the eye, which is normally protected by the blood-ocular barriers (i.e., blood-aqueous humor and blood-retinal barriers), it is preferred that the antagonist be able to cross these barriers to reach the site of action. Alternatively, the antagonist could be given intraocularly or periocularly by an acceptable method to deliver the antagonist to its site of action. All modes of delivery that result in placing the antagonist at its site of action are contemplated.

In general, the antagonists useful in the present invention will be administered orally. Daily dosage of these compounds will range between about 0.1 and about 500 milligrams (mg), preferably between about 5 and about 100 mg. Local administration of these compounds will require a dosage range of between about 0.1 and about 50 mg, preferably between about 0.5 and about 5 mg. An aqueous composition will generally contain between about 0.1 and about 10 percent by weight (wt%) of the active, preferably between about 1 and about 5 wt%.

I Claim:

1. A composition for treating diabetic retinopathy comprising a pharmaceutically effective amount of an antagonist of glutamate-induced excitotoxicity.

2. The composition of Claim 1 wherein the antagonist is selected from the group consisting of polyamine site antagonists, NMDA receptor antagonists, and channel blockers which operate uncompetitively to block the NMDA receptor channel.

3. The composition of Claim 2 wherein the antagonist is a polyamine site antagonist.

4. The composition of Claim 3 wherein the polyamine site antagonist is eliprodil.

5. A method for treating diabetic retinopathy which comprises, administering a pharmaceutically effective amount of an antagonist of glutamate-induced excitotoxicity.

6. The method of Claim 5 wherein the antagonist is selected from the group consisting of polyamine site antagonists, NMDA receptor antagonists, and channel blockers which operate uncompetitively to block the NMDA receptor channel.

7. The method of Claim 6 wherein the antagonist is a polyamine site antagonist.

8. The method of Claim 7 wherein the polyamine site antagonist is eliprodil.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 98/21423

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K31/165 A61K31/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 521 215 A (KLOOG YOEL ET AL) 28 May 1996	1,2,5,6
Y	see column 6, line 30 - line 39 see column 7, line 19 - line 33 see column 9; table 1	3,4,7,8

X	FR 2 738 568 A (SYNTHELABO) 14 March 1997	1-3,5-7
Y	see page 19, line 36 - line 39 see page 20, line 21 - line 22 see page 22, line 8 - line 10 see page 22, line 26 - line 27	4,8

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Y	see page 2, line 26 - line 28 see page 5, line 1 - line 14 see example 5	3,4,7,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 97 01339 A (ALLERGAN INC) 16 January 1997 see page 10, line 5 - line 10 see page 10, line 30 - page 11, line 8 see example 1 see claim 4 see figure 1	1,2,5,6
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